REMARKS

In the action, the examiner rejected claims 17-19, 21 and 58-62 under 35 U.S.C. §103(a) as obvious in view of Pardridge (*Nature Rev. Drug Disc.* 1:131-39, 2002, hereinafter "Pardridge"), in view of Fillebeen, (*J Biol Chem*, 274:7011-17, 1999, hereinafter "Fillebeen"), and Neels et al. (*J Biol Chem* 274:31305-311, 1999, hereinafter "Neels") and Saenko, WO00/71714, (hereinafter "Saenko"). The examiner objected to claims 17 and 18 for informalities. Reconsideration is requested in view of the amendments and arguments herein.

I. Support for the Amendment to the Claims

Support for the amendment to the claims can be found throughout the specification, for example, at page 3, line 24, which discloses that the receptor associated protein is termed RAP. The amendment includes no new matter.

II. The rejection under 35 U.S.C. §103(a) should be withdrawn

The examiner rejected the pending claims under 35 USC §103(a) asserting that it would have been obvious to combine the disclosures of Pardridge, Fillebeen, Neels and Saenko to arrive at the present invention. The examiner asserts that because the art (*e.g.*, Neels, Fillebeen, Saenko) teaches that the LRP molecule binds to and endocytoses several of its ligands, LRP necessarily transcytoses the ligand RAP across the cell membrane, and therefore related receptor LRP2 must also trancytose RAP. The examiner also asserts that because Saenko teaches that LRP can bind amino acids 203-319 of the RAP molecule (see Saenko), the LRP2 receptor also necessarily binds RAP at the same sequence due to the common structure of RAP and the homology of the LRP and LRP2 receptors. Without explaining how the teachings of the art can be extrapolated to support any further assertions, the Examiner also asserts that fragments of RAP as claimed would be transported across the blood brain barrier (BBB), and that the art renders obvious administration of fragments of RAP conjugated to a diagnostic or therapeutic agent in order to increase transport of the agents across the BBB.

Applicants respectfully disagree. For the reasons discussed below, the factual assumptions on which the obviousness rejection is based are not supported by the evidence cited. Moreover, there are multiple unexplained gaps in the scientific reasoning supporting the rejection. One cannot extrapolate data obtained using one ligand to predict the behavior of

another unrelated antagonist ligand (*e.g.*, from lactoferrin to RAP), or from one receptor to another receptor (*e.g.*, from LRP to LRP2), or from one activity (internalization and degradation within a cell) to another activity (transport across the BBB without internalization and degradation).

The pending claims are directed methods of treating individuals comprising administration of a conjugate comprising a polypeptide consisting of a RAP portion having an amino acid sequence at least 80% identical to amino acids 221-323 of SEQ ID NO: 1, and which binds to megalin (LRP2).

Pardridge discloses that receptor mediated transport pathways may be useful to transport therapeutics (*e.g.*, BDNF) across the BBB using chimeric peptides that bind to a BBB receptor. Pardridge does not address LRP, LRP2 or RAP. In particular, Pardridge does not disclose or suggest that RAP is transcytosed across the BBB, does not teach that RAP might be transcytosed by LRP or LRP2, or that RAP may be used in a chimeric protein to mediate transport of a therapeutic agent. The Examiner acknowledges at page 4 that "Pardridge does not teach conjugates comprising RAP fragments, as recited in independent claims."

Fillebeen shows that lactoferrin is transcytosed across the BBB but does not disclose or suggest that RAP, an entirely different and unrelated protein, is transcytosed across the BBB. Fillebeen only speculates that lactoferrin is transported across the BBB by LRP, based on data that RAP blocks transcytosis of lactoferrin across the BBB. Fillebeen's speculation is inconsistent with other reports, e.g. Faucheux et al., *Proc. Nat'l. Acad. Sci. (USA)* 92:9603-9607 (1995) (Exhibit A hereto), that *lactoferrin receptor* (a different receptor than LRP) transports lactoferrin and iron across the BBB.

Even if one assumes, *arguendo*, that LRP is the receptor responsible for transport of lactoferrin across the BBB, the Examiner is mistaken in concluding that one of ordinary skill in the art would predict that other LRP ligands would be transported across the BBB. Fillebeen states that LRP binds to and is responsible for internalization of many ligands, including chylomicrons, Lf, alpha2-macroglobulin, *Pseudomonas* exotoxin, proteinases and proteinase-inhibitor complexes. The factual assumption at page 6 that "this receptor [LRP] transports [any or all] molecules across the BBB" is not supported by the cited evidence. There would not be a

reasonable expectation that any and all of these diverse LRP ligands would be transported across the BBB.

Moreover, data with respect to lactoferrin is not extrapolatable to RAP because RAP is an *antagonist* of LRP and binds to LRP in a manner unlike any other LRP ligand. See, *e.g.*, Neels abstract which states that "RAP binding to LRP induces a conformational change in the receptor that is incompatible with ligand binding." See also Vash et al. (*Blood* 92:3277-85, 1998) (Exhibit B hereto) noting that RAP appears to cause a conformational change in the LRP protein preventing it from binding other ligands, thereby, rendering RAP the universal antagonist (see Vash, page 3277, 1st col.).

For these reasons, Fillebeen does not teach or suggest to one of ordinary skill in the art that RAP, or fragments or mutants of RAP, would be transported across the BBB. In addition, Fillebeen neither discloses nor suggests that LRP transports RAP across the BBB, nor that LRP2 transports RAP across the BBB. Thus, Fillebeen does not disclose or suggest a RAP fragment polypeptide at least 80% homologous to amino acids 221-323 of SEQ ID NO: 1 that retains LRP2 binding. The Examiner acknowledges at page 5 of the Action that Fillebeen "does not explicitly teach administration of conjugates comprising RAP for increasing transport across the BBB and does not teach conjugates comprising RAP fragments. . ."

Neels discloses that LRP binds a diverse array of ligand types. Neels states that "LRP can bind and internalize a diverse spectrum of structurally unrelated ligands in a calcium-dependent manner including apolipoproteins, lipases, proteinases, proteinase-inhibitor complexes…..," and discloses binding of RAP to LRP. Neels provides data on binding of LRP fragments to various ligands, but provides no data regarding internalization of ligands into any cell type. Neels provides no data on transport across the BBB. Neels neither discloses nor suggests that any or all of the diverse ligands of LRP can be transcytosed across the BBB, nor that RAP binds to the LRP2 receptor and is transcytosed across cell membranes. Further, Neels does not disclose or suggest the RAP fragment polypeptides recited in the claims which retain binding to LRP2. The Examiner acknowledges at page 5 that "Neels does not teach administration of conjugates comprising RAP for increasing transport across the BBB and does not teach conjugates comprising RAP fragments . . ."

Saenko teaches use of a RAP polypeptide to inhibit Factor VIII uptake by the LRP (LRP1) receptor, which is a different receptor from LRP2 recited in the pending claims. Saenko teaches that RAP inhibits FVIII binding to LRP1 and teaches that residues 203-319 of RAP bind LRP, but the Examiner admits that Saenko does not teach administration of conjugates comprising this fragment to subjects. Saenko also does not teach that this fragment would be transported across the BBB. Furthermore, Saenko does not disclose that RAP is taken up by the LRP1 receptor, or that RAP binds to LRP2, and certainly does not teach that the particular fragment of RAP disclosed in Saenko binds to LRP2.

The Examiner's factual assumption at page 6 that regions of RAP that bind LRP will also bind LRP2 is not supported by the cited evidence. Given the atypical binding characteristic of RAP with LRP, a person of ordinary skill would not have reasonably predicted that the same RAP sequence that bound LRP in an unconventional arrangement would inherently bind LRP2. The two receptors are highly divergent in sequence, as well as biodistribution, ligands to which they bind and, importantly, in trafficking behavior. The attached sequence alignment (Exhibit C hereto) shows that LRP and LRP2 share only approximately 40% homology over the entire span of the protein. Additionally, the ligand binding domain 1 of LRP1 is significantly different than that of LRP2, which exhibits seven ligand binding repeats in this domain instead of two as in LRP1, and the cytoplasmic domains of the proteins, which confers much of the functionality, are significantly different (Marzolo et al., *Traffic* 4:273-88, 2003) (Exhibit D hereto).

Moreover, the two receptors have distinct functions in vivo. The art has not suggested that the two proteins are interchangeable, or that all ligands that bind LRP necessarily bind LRP2 due to the asserted high homology between the two receptors. See also page 36, lines 9-26, and page 41, line 1, to page 42, line 7, of the specification which disclose that LRP and LRP2 bind different ligands, illustrating that not all LRP ligands bind LRP2 and *vice versa*, and implying that the alleged high homology between the receptors alluded to by the examiner does not necessarily confer similar binding capacity and function. In fact, Orlando et al., *Proc. Nat'l. Acad. Sci. (USA)* 91:3161-3165 (1994) (Exhibit E hereto) suggest that megalin (gp330) binds to entirely different regions of RAP.

The specification and the art also teach that LRP and LRP2 are found on distinct cell types (page 34, lines 21-32, and page 35, lines 28-30) and as such, do not necessarily overlap in

their functions. Marzolo et al. (*supra*) teaches that the LRP1 and LRP2 receptors are expressed on different sides of the polarized endothelial cell membranes which is relevant to function and transport of proteins by the receptors. For example, LRP1 is expressed basolaterally in polarized cells such as brain endothelium (*i.e.*, on the brain side of the membrane), while LRP2 is apically expressed in polarized brain endothelium (*i.e.*, on the blood side f the membrane). To effectively modulate blood to brain transport as required by the claims, receptor expression must be on the apical side of the membrane to bind ligand in the blood and transport it into the brain. Based on the basolateral expression pattern of LRP1, one of ordinary skill in the art would not predict that LRP1 transports any ligand from blood to brain across the BBB.

To establish a *prima facie* case of obviousness, the examiner must show that all the elements of the claim are taught or suggested in the prior art (MPEP 2143.03 and Federal Register Examination Guidelines for Determining Obviousness, Section III.A.1, Fed Reg., Vol 72, No. 195, 2007), and if prior art elements are described in the art, the combination of elements must yield predictable results to render a clamed invention obvious. Further, it should be demonstrated that the prior art reference(s) provide a teaching, suggestion or motivation to combine the references, and/or there is a reasonable expectation of success (MPEP 2142 and Federal Register Examination Guidelines for Determining Obviousness, Section III.G, Fed Reg., Vol 72, No. 195, 2007).

Pardridge, Fillebeen, Neels and Saenko are improperly combined because they each deal with different receptors than that recited in the claims, and transport of ligands other than RAP as recited in the claims. These ligands and receptors are not shown in any of the cited references to be equivalent or interchangeable. Even if combined, the references do not disclose or suggest that RAP would be transported across the BBB, or that domain 3 of RAP, without domains 1 and 2, would be transported across the BBB. The Examiner acknowledges that none of the references teach administration of conjugates comprising the RAP fragment recited in the claims to increase transport across the BBB, and does not appear to dispute that the cited art fails to disclose that LRP2 (megalin) mediates transport across the BBB. Therefore, the cited art fails to teach all elements of the claims.

Additionally, the cited art does not provide a reasonable expectation of success that RAP would be transported across the BBB, or that domain 3 of RAP, without domains 1 and 2,

would be transported across the BBB. There is no data showing transport of RAP or any fragments of RAP across the BBB. One of ordinary skill in the art would not conclude from the data in Fillebeen (in which RAP inhibited lactoferrin transcytosis by an unknown receptor), that LRP1 was responsible for transporting lactoferrin in view of the known fact that RAP binds multiple receptors besides LRP1, and the fact that LRP is expressed on the wrong side of the BBB (See Marzolo et al., *supra*). For reasons explained below, even if Fillebeen does teach that lactoferrin crosses the BBB, one of ordinary skill in the art would not reasonably predict that an LRP antagonist like RAP would cross the BBB.

Also, even if Neels teaches that RAP binds some fragments of LRP, one of ordinary skill in the art would not reasonably predict that RAP is transported across the BBB based on the teaching in the cited art which are devoid of reference to RAP trancytosis by any receptor. Even if Saenko teaches that amino acids 203-319 of RAP bind LRP, one of ordinary skill in the art would not reasonably predict that RAP or any fragment thereof would be transported across the BBB. Further, one of ordinary skill reading the cited references, none of which refer to the LRP2 receptor as one that mediates ligand transcytosis, would not reasonably predict that LRP2 would mediate transcytosis of RAP fragments across the BBB.

Moreover, RAP was considered a ligand of LRP in the sense that it bound to LRP, but was generally held in the art to be an antagonist to all ligands that bind LRP, and was more referred to as an antagonist of LRP than a ligand, *per se* (see *e.g.*, Vash et al.). In fact, Herz et al., (*J Clin. Invest* 108:779-84, 2001) (Exhibit F hereto) fails to list RAP in a figure describing LRP ligands and their LRP-binding specificity (Figure 1). RAP instead acts as a chaperone to the newly translated LRP and prevents LRP degradation. As such, a person of ordinary skill would not have expected RAP to be transcytosed by LRP as it was not seen as an activator of LRP function, it was not equivalent to other LRP binding molecules, and it served no other function but to chaperone LRP intracellularly. Therefore, based on the RAP function in the cell, one of ordinary skill would not predict that RAP would be transcytosed by LRP, and would not have reasonably predicted that either LRP or LRP2 would transport RAP across the BBB.

Thus, the examiner has not established a *prima facie* case of obviousness with respect to the present claims because (1) not all elements are disclosed by the cited art, even when combined, and as such, the claimed invention was unpredictable until the present disclosure, and

(2) the cited art does not provide a reasonable expectation of success in carrying out the claimed method. Therefore, the present invention is not obvious in light of Pardridge, Fillebeen, Neels and Saenko and the rejection under 35 U.S.C. §103(a) should be withdrawn.

III. Conclusion

Applicants submit that the application is in condition for allowance and respectfully request notification of the same.

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Respectfully submitted,

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